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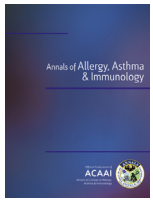

Perspectives

A critical appraisal of omalizumab as a therapeutic option for chronic refractory urticaria/angioedema

David M. Lang, MD

Department of Allergy and Clinical Immunology, Cleveland Clinic, Respiratory Institute, Cleveland, Ohio

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The Clinical Problem

Despite advances that have been made in our understanding of chronic urticaria/angioedema (CUA), many patients with CUA continue to experience poor control of their disease and severe impairment in their quality of life.[1,2] More than half of patients may not achieve satisfactory control of CUA with antihistamine treatment.[1,3] Urticaria and pruritus are promoted primarily by the action of histamine on H_1 receptors located on endothelial cells (wheal) and on sensory nerves (flare); however, CUA is characterized by a nonnecrotizing perivascular infiltrate of $CD4^+$ lymphocytes, monocytes, neutrophils, eosinophils, and basophils that can be recalcitrant to antihistamine therapy—even when advanced to high doses.[1] Patients with CUA who do not respond to combination antihistamine therapy, with or without an antileukotriene, including dose advancement of a potent antihistamine (eg, doxepin at a dose of 75-125 mg/d) as tolerated, are considered to have antihistamine-resistant or refractory CUA.[4]

A number of therapeutic agents have been reported to be efficacious in patients with refractory CUA in case reports or case series.[5,6] However, such studies may be subject to bias and do not provide high-quality evidence.[7] Randomized controlled trials tend to be rated as high-quality evidence; however, the quality of evidence may be lowered based on methodologic issues and other factors.[8] Of the 4 agents for which randomized controlled trials in patients with refractory CUA have been reported (hydroxychloroquine,[9] stanozolol,[10] cyclosporine,[11,12] and omalizumab[13–16]), cyclosporine and omalizumab are the only agents for which more than one randomized controlled trial has been published. In the 2014 update of the Urticaria/Angioedema Practice Parameter,[4] a critical appraisal of the literature supporting the therapeutic utility of cyclosporine judged this evidence to be of low quality based on a number of methodologic shortcomings, leading to a weak recommendation for use of cyclosporine for refractory CUA. The weak recommendation does not imply that cyclosporine may not be of benefit in properly selected patients with refractory CUA or that it should not be prescribed. The weak recommendation signifies the need for clinicians to carefully consider whether administration of cyclosporine is favorable from the standpoint of balancing the potential for benefit with the potential for harm and discuss this with patients to determine that the decision to proceed with a trial of cyclosporine is consistent with their values and preferences.

Omalizumab is a recombinant humanized monoclonal antibody approved by the US Food and Drug Administration (FDA) in 2003. It is the first monoclonal antibody approved for patients with allergic disorders. Omalizumab interrupts the allergic response at its primary step: the binding of allergen-specific IgE to mast cells.[17] Its mechanism of action for asthma is thought to entail reduction of free IgE combined with down-regulation of expression of the high-affinity IgE receptor on basophils and mast cells.[17] Salutary response to omalizumab in patients with refractory asthma has exhibited a gradual pattern of onset: 38% responding in 4 weeks and 62% after 16 weeks.[18,19] This Clinical Perspective is intended to critically appraise the published evidence on omalizumab as a therapeutic intervention for patients with refractory CUA.

Evidence

Observational Studies

Improvement of refractory CUA in association with administration of omalizumab has been described in a number of observational studies. In some case reports or case series, omalizumab was dosed according to the FDA-approved label for moderate-severe persistent asthma[20–25] based on total IgE level and body weight[17]; in other reports, omalizumab was administered via a

Reprints: David M. Lang, MD, Division of Allergy/Immunology, Cleveland Clinic, 9500 Euclid Ave, A90, Cleveland, OH 44195; E-mail: langd@ccf.org.

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"one size fits all" strategy,[25,26] using a fixed dose of omalizumab administered every 2 or 4 weeks.

Several reports also described improvement of refractory physical urticaria or angioedema syndromes with omalizumab, including cholinergic urticaria,[25,27] cold urticaria/angioedema,[25,28,29] delayed pressure urticaria/angioedema,[25,30] dermatographia,[25,31] and solar urticaria.[25,29,32]

Most but not all[29,33] patients in the above reports benefited from omalizumab, as reflected in lower levels of symptoms and medication reliance. In some patients, omalizumab was associated with complete remission of symptoms.[25] In contrast to benefit in patients with asthma, salutary response to omalizumab was observed promptly—in some cases within days.[22,25,26,28,30,34] These reports set the stage for conducting randomized controlled trials to evaluate the hypothesis that omalizumab is efficacious and safe for patients with refractory CUA.

Randomized Controlled Trials

Ninety individuals were enrolled in a randomized, double-blind, placebo-controlled study[13] in which a single dose of 75, 300, or 600 mg of omalizumab or placebo was administered. Participants in this study had CUA that was poorly controlled despite treatment with H_1-antihistamines. Participants who received either 300 or 600 mg of omalizumab exhibited statistically significant improvement compared with placebo.

A second randomized, double-blind, placebo-controlled study enrolled 49 individuals with CUA and IgE autoantibodies to thyroperoxidase.[14] After 24 weeks, those randomized to omalizumab demonstrated statistically significantly greater reduction in urticaria activity score; 59% of those randomized to omalizumab were symptom free compared with 14% receiving placebo.

In a third double-blind study of patients with CUA poorly controlled with H_1-antihistamines, 323 were randomized to 3 subcutaneous injections of omalizumab at 4-week intervals (75 mg, 150 mg, or 300 mg) or placebo followed by a 16-week observation period.[15] Efficacy analyses were performed using data from a modified intent-to-treat population that included individuals who were randomized and received at least one dose of either omalizumab or placebo. The primary end point: itch severity score, urticaria activity score (UAS) and other prespecified secondary end points, were significantly improved ($P < .001$) after 12 weeks in individuals randomized to 150-mg and 300-mg doses compared with placebo. In post hoc analyses at week 12, the proportions of individuals who were free of hives and itching (ie, UAS-7 of 0) were 5% in those randomized to placebo and 16%, 22%, and 44%, respectively, in those randomized to omalizumab at doses of 75 mg, 150 mg, and 300 mg. This leads to a calculated number needed to treat (NNT) for being hive free and itch free in association with receiving omalizumab at doses of 150 or 300 mg for 12 weeks of 5.9 and 2.6. In other words, approximately 1 in 6 or 1 in 3 individuals, respectively, who receive omalizumab at doses of 150 or 300 mg for 12 weeks will experience benefit consisting of being hive free and itch free. The rate of serious adverse events observed in individuals randomized to 300 mg, which included melena, nephrolithiasis, and urticaria, was higher (6%) than the rates observed in those randomized to 150 mg (1%), 75 mg (1%), or placebo (3%); however, a number of the adverse events in this study were observed during the follow-up period when omalizumab administration had been suspended.

In a fourth randomized controlled study, 336 of 480 patients screened for participation, whose CUA remained poorly controlled despite advancement of H_1-antihistamines to 4 times the FDA-approved dose in combination with H_2-antihistamines and/or an antileukotriene,[16] received 6 injections of 300 mg of omalizumab or placebo on a monthly basis. Patients maintained their prerandomization regimens of high-dose H_1-antihistamine, H_2-antihistamine, and/or antileukotriene during the treatment period of the study. The primary objective of this study was to assess safety. Efficacy was assessed at 12 and 24 weeks. Statistically significant benefit was observed in patients randomized to omalizumab compared with placebo for itch severity score at 12 weeks ($P < .001$) and for other outcome measures. Figure 1 displays the weekly itch severity scores during the study and illustrates the prompt benefit in patients randomized to 300-mg monthly doses of omalizumab compared with placebo. No remarkable differences in adverse or severe adverse events were reported in patients receiving omalizumab compared with placebo.

An aspect of the design of this fourth randomized controlled trial is important to emphasize. The patients enrolled in this study had poorly controlled CUA despite combination pharmacotherapy. The patients enrolled in randomized controlled studies of omalizumab for CUA had a high disease burden, with a mean UAS-7 of 31, and a history of prior corticosteroid treatment for CUA in approximately 50%.[35] However, the external validity of the findings from the 3 previously described randomized controlled trials[13–15] can be impugned based on the lack of a protocol for preenrollment systematic escalation of antihistamine treatment to eliminate those whose condition was not truly antihistamine resistant. This methodologic shortcoming, known as "indirectness,"[36] is one of the reasons the Practice Parameter on Urticaria/Angioedema[4] determined that cyclosporine merits a weak recommendation for patients with refractory CUA. Patients enrolled in this fourth randomized controlled trial[16] also maintained combination pharmacotherapy during study participation. In the other randomized trials of omalizumab,[13–15] the comparator treatment was cetirizine at a daily dose of 10 mg. Inadequate dose titration of an efficacious comparator treatment is also a methodologic concern because it can lead to a potentially misleading claim of effectiveness.[8] On the basis of its design features, this fourth randomized controlled trial[16] enhances the strength of evidence supporting the efficacy of omalizumab for patients with refractory CUA.

Areas of Uncertainty

A number of questions await further clarification concerning omalizumab as a therapeutic intervention for refractory CUA. Not all patients with refractory CUA experience benefit with initiation of omalizumab treatment. At this time, the potential for a salutary response cannot be predicted based on demographic

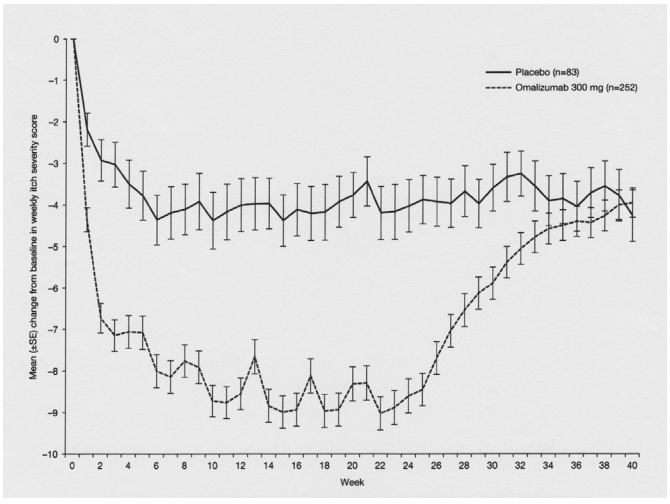

Figure 1. Mean change from baseline in itch severity scores in patients with refractory chronic urticaria/angioedema randomized to omalizumab or placebo. Data are reproduced with permission from Kaplan et al.[16]

characteristics (eg, age and sex); laboratory data, including findings that reflect autoimmunity (eg, autologous serum skin test, autologous plasma skin test, autoantibodies to IgE or the high-affinity IgE receptor, or antithyroid antibodies); histopathologic findings; biomarkers; or the nature or previous course of CUA.[37]

The mechanism of action for benefit in association with omalizumab is currently not understood.[1] The marked benefit that may occur in only several days is too rapid a response to be explained on the basis of receptor down-regulation, although such an effect may participate in maintaining benefit. It is possible the mechanism of action involves an effect on basophil function, which is abnormal in CUA.[38] This is an important area for further study. Determining the mechanism by which omalizumab is efficacious for refractory CUA may provide clues to the subgroups of patients with refractory CUA most likely to benefit, optimal dosing, and duration of treatment.

The rate of anaphylaxis observed in patients with severe refractory asthma receiving omalizumab is approximately 1 in 1,000.[17,39] Protocols for omalizumab administration stipulate a wait time of 2 hours for the first 3 doses and 30 minutes for each subsequent dose.[39] Patients with severe refractory allergic asthma who are candidates for omalizumab may be more likely to become sensitized to a medication than patients with refractory CUA. Whether the rate of anaphylaxis will be similar in patients with CUA and whether the same precautions for omalizumab are appropriate for a population of patients with CUA are unclear at this time.

The data presented suggest greater efficacy for 300 mg every 4 weeks; however, adverse reactions were observed more frequently at this dose compared with 150 mg every 4 weeks.[15] A prudent approach may be to initiate a therapeutic trial at a dose of 150 mg every 4 weeks and, if this lacks efficacy, to proceed with dose advancement to 300 mg every 4 weeks. Alternatively, an initial dose of 300 mg every 4 weeks can be administered, with a step down to 150 mg every 4 weeks after clinical improvement has been observed. Additional studies are required to clarify the optimal dose of omalizumab to prescribe for refractory CUA.

Individuals with physical urticaria or angioedema syndromes were excluded from the randomized controlled trials described above.[13-16] Because the data describing benefit with omalizumab derive from case reports and case series, the quality of evidence supporting administration of omalizumab for patients with physical urticaria/angioedema syndromes is not high quality. The therapeutic utlity of omalizumab for this subgroup remains an area for additional investigation in randomized controlled trials. At this time, the decision to prescribe omalizumab for patients with physical urticaria/angioedema syndromes should be approached from an individualized standpoint, with a careful assessment of the potential for harm and burden compared with the potential for benefit, and should entail the patient expressing his/her values and preferences and participating in the medical decision-making process.

Similar to the experience with omalizumab in patients with refractory asthma, anti-IgE therapy carries the potential to significantly alter the course of disease for patients with refractory CUA; however, because patients with refractory asthma and refractory CUA experienced recrudescence of symptoms after stopping omalizumab therapy in association with clinical trial termination (Fig 1), continued administration of omalizumab is required to perpetuate improvement or remission.[14,15,17] Asthma is a lifelong condition. In contrast, the course of CUA may span months or years.[40] The optimal duration of omalizumab treatment for CUA and optimal strategies for suspending omalizumab also merit clarification in future studies.

Conclusions and Recommendations

The efficacy of omalizumab for refractory CUA has been supported by several randomized controlled trials and observational studies. The evidence for efficacy is more robust with omalizumab than with all other agents heretofore described in case series, case reports, or randomized trials of patients with refractory CUA. The calculated NNTs for omalizumab administered for refractory CUA for 12 weeks at doses of 150 and 300 mg, respectively, of 5.9 and 2.6 for becoming hive free and itch free[15] compare favorably with therapeutic agents commonly prescribed for patients with asthma based on best evidence. These comparisons include calculated NNTs for low-dose inhaled corticosteroids[41] for reducing the rate of severe exacerbations in patients with mild asthma during 1 year (NNT = 5.0) and low-dose inhaled corticosteroid combined with long-acting β-agonist for reducing the rate of severe exacerbations, compared with medium-dose inhaled corticosteroids, in patients with moderate persistent asthma during 1 year (NNT = 7.6).

Omalizumab has been well tolerated by patients with refractory CUA and is associated with less potential for harm compared with other therapeutic alternatives (eg, calcineurin inhibitors) for refractory CUA. Although its administration does not entail the burden of undergoing serial phlebotomies, individuals prescribed omalizumab will be required to receive subcutaneous injections on a monthly basis in a medical setting and to be observed afterward, and will need to obtain and carry injectable epinephrine in association with drug administration.

Omalizumab is costly. Formal economic models using cost utility (cost per quality-year of life gained) and cost-effectiveness (cost per attack prevented) analyses will be helpful to aid allergists/immunologists in clarifying appropriate patient selection for omalizumab in the treatment of refractory CUA.

In many cases, CUA can be controlled with administration of second-generation antihistamine medications, and if still symptomatic, control can be achieved with regular use of combination therapy with H_1-antihistamine medications, advanced to maximally tolerated doses, and H_2-antihistamine with or without an antileukotriene agent.[4] Omalizumab has become the best-studied agent for treatment of refractory CUA and the agent for which the data in support of its efficacy are most methodologically sound. Omalizumab is an effective therapeutic option for patients with refractory CUA and can significantly improve outcomes in this challenging subgroup of patients.

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